NICE advice

Parkinson's disease with motor fluctuations: safinamide

Evidence summary
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Key points

The content of this evidence summary was up-to-date in February 2017. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Regulatory status: New medicine. Safinamide is a monoamine oxidase-B (MAO-B) inhibitor. It received a European marketing authorisation in February 2015 and was launched in the UK in May 2016. It is licensed for treating mid- to late-stage idiopathic Parkinson's disease in adults who are experiencing motor fluctuations, as an add-on treatment to a stable dose of levodopa when used either on its own or in combination with other Parkinson's disease medicines.

Overview

This evidence summary discusses 3 randomised controlled trials (RCTs) in people with Parkinson's disease of at least 3 years duration, who were taking a stable dose of levodopa and were experiencing motor fluctuations. Most people in the studies were also taking other Parkinson's disease medicines, most commonly a dopamine agonist. There is limited data on the use of safinamide as a first choice add-on treatment to levodopa.

The main clinical benefits of safinamide at 24 weeks were an increase in 'on time' without troublesome dyskinesia (involuntary movements) of approximately 30 to 60 minutes daily, and a

similar reduction in 'off time', compared with placebo. This effect was still observed at a 2-year follow-up.

Dyskinesia was the most commonly reported adverse effect, but was usually mild and associated with an increase in on time. Contraindications and cautions for use are similar to those of other MAO-B inhibitors. There is a potential risk of retinal degeneration in people with, or a previous history of, retinal disease with safinamide.

Safinamide is the third MAO-B inhibitor licensed in the UK as add-on treatment to levodopa in people with Parkinson's disease who are experiencing motor fluctuations. It is more expensive than other MAO-B inhibitors: 30-day treatment costs are £3.38, £9.67 and £69.00 for rasagiline, selegiline and safinamide respectively (Drug Tariff, February 2017; excluding VAT).

There are no head-to-head studies comparing the efficacy and safety of safinamide with other active treatments, including other MAO-B inhibitors. The NICE guideline on Parkinson's disease makes recommendations on the place in therapy of adjuvant treatments. The choice of treatment will depend on the person's clinical and lifestyle characteristics, and their preferences, after an informed discussion about the benefits and risks of treatment.

A framework to inform local decision-making is shown in table 1.

Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications

Effectiveness

- Safinamide was more effective than placebo at improving on time without troublesome dyskinesia by approximately 30 to 60 minutes daily (from a baseline of about 9 hours daily) at 24 weeks and 2 years follow-up. There were similar reductions in off time (3 RCTs: study 016, SETTLE study, study 018, total n=1,218).
- Safinamide did not improve dyskinesia in the 3 RCTs (measured by DRS total score) compared with placebo. This was the primary outcome of study 018.
- In study 016 and SETTLE, safinamide improved motor symptoms during on time (by about 2 points on UPDRS-III) compared with placebo at 24 weeks (from a baseline of 22 to 29 points). This improvement was still observed at 2 years only in the safinamide 100 mg daily group.
- Safinamide 100 mg or 50–100 mg was more effective than placebo at improving health-related quality of life (measured by PDQ-39). There was no statistically significant difference between safinamide 50 mg and placebo (3 RCTs).
- More people had improvement in clinical global impression (measured by CGI-C) with safinamide compared with placebo at 24 weeks; this was statistically significant. This difference was still observed at 2 years only in the safinamide 50 mg daily group.

Safety

- The SPC states that safinamide is contraindicated in severe hepatic impairment and should be used with caution in moderate hepatic impairment.
- Safinamide is also contraindicated in people with albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy; and with other MAO inhibitors or pethidine.
- The SPC states that safinamide used as an adjunct to levodopa may potentiate the adverse effects of levodopa, and pre-existing dyskinesia may be exacerbated.

Patient factors

- Common adverse effects reported in the SPC are dyskinesia, insomnia, nausea, somnolence, dizziness, headache, Parkinson's disease symptoms, cataracts, orthostatic hypotension and falls.
- Impulse control disorders have been seen with other MAO inhibitors, and patients and carers should be made aware of the behavioural symptoms of these.
- Safinamide can be used without any dietary tyramine restrictions.
- Safinamide has not been investigated in people with severe, disabling peak dose or biphasic dyskinesia with unpredictable or wide fluctuations; people with a history or presence of retinal disease; or people with psychiatric illness, bipolar disorder or severe depression.

Resource implications

- The NHS list price for safinamide 50 mg or 100 mg is £69.00 for 30 tablets (Drug Tariff, February 2017; excluding VAT).
- The 30-day cost of other MAO-B inhibitors is £3.38 for rasagiline 1 mg daily and £9.67 for selegiline 10 mg daily (Drug Tariff, February 2017; excluding VAT).

Introduction and current guidance

A NICE guideline on Parkinson's disease was published in June 2006. An update of this guideline is in progress and publication is expected in April 2017. The guideline describes Parkinson's disease as a progressive neurodegenerative condition resulting from the death of dopamine containing cells of the substantia nigra region of the brain.

As Parkinson's disease progresses, most people will develop motor symptoms and will need levodopa treatment. During the course of the disease motor fluctuations and dyskinesias occur, which may be related to long-term levodopa use or disease progression, or both. Adjuvant treatments may also be needed for people whose Parkinson's disease is not adequately controlled on levodopa alone, with the aim of reducing motor complications and improving quality of life. These include dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors and catechol-O-methyl transferase (COMT) inhibitors.

The NICE guideline (2006) states that it is not possible to identify a universal first-choice adjuvant treatment for people with later Parkinson's disease. The choice of adjuvant medicine first prescribed should take into account:

- clinical and lifestyle characteristics
- patient preference, after the patient has been informed of the short- and long-term benefits and drawbacks of the classes of medicines.

It recommends that MAO-B inhibitors may be used to reduce motor fluctuations in people with later Parkinson's disease.

Product overview

Mode of action

The summary of product characteristics (SPC) states that safinamide (Xadago: Profile Pharma) is a highly selective and reversible MAO-B inhibitor. This differs from rasagiline and selegiline which are selective and irreversible MAO-B inhibitors (European Public Assessment Report [EPAR]: Xadago). Several other mechanisms of action of safinamide have been identified by in-vitro data, including sodium channel inhibition and reducing excessive glutamate release. However, the extent to which the non-dopaminergic effects contribute to the overall clinical effect of safinamide has not been established. The EPAR for safinamide states that no clinical effects that might be related to these mechanisms were clearly evident in clinical trials.

Regulatory status

Safinamide is a new medicine that received a European marketing authorisation in February 2015 and was launched in the UK in May 2016. It is licensed for treating mid-to late-stage idiopathic Parkinson's disease in adults who are experiencing motor fluctuations, as add-on treatment to a stable dose of levodopa alone or in combination with other Parkinson's disease medicines (SPC: safinamide).

Dosing information

The SPC for safinamide states that treatment should be started at a dose of 50 mg once daily. This may be increased to 100 mg once daily on the basis of individual clinical need. No dose adjustment is required in people with mild hepatic impairment, but the lower dose of 50 mg daily is

recommended for people with moderate hepatic impairment. Safinamide is contraindicated in people with severe hepatic impairment.

Cost

Safinamide 50 mg tablets and 100 mg tablets cost £69.00 for 30 tablets (Drug Tariff, February 2017; excluding VAT).

Evidence review

A literature search was conducted which identified 151 references (see search strategy for full details). These references were screened using their titles and abstracts and 14 references were obtained and assessed for relevance.

Two randomised controlled trials (RCTs) identified from the search (Borgohain et al. 2014a [study 016] and Borgohain et al. 2014b [study 018]) were included in this evidence summary. An additional 24-week RCT (Schapira et al. 2016 [SETTLE study]) which was considered by the European Medicines Agency during the regulatory process and was published after the search was conducted was also included. A summary of the included studies is shown in table 2 (see evidence tables for full details).

Table 2 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Borgohain et al. 2014a (study 016) RCT	Mid to late Parkinson's disease (≥3 years) with motor fluctuations (n=669)	Safinamide 50 mg or 100 mg daily vs placebo	Change in mean daily on time without troublesome dyskinesia
Borgohain et al. 2014b (study 018) RCT	Mid to late Parkinson's disease (≥3 years) with motor fluctuations (n=669[a])	Safinamide 50 mg or 100 mg daily vs placebo	Change in mean DRS total score during on time

Schapira et al. 2016 (SETTLE study) RCT	Parkinson's disease (≥3 years) with motor fluctuations (n=549)	Safinamide 50 mg to 100 mg daily vs placebo	Change in mean daily on time without troublesome dyskinesia
[a] Study 018 was an 18-month extension of study 016. 669 participants were randomised; 544 participants enrolled into study 018.			
Abbreviations: DRS, Dyskinesia Rating Scale; RCT, randomised controlled trial.			

The remaining 12 references were excluded. These are listed in excluded studies with reasons for their exclusion.

Clinical effectiveness

This evidence summary is based on 3 double-blind, placebo-controlled RCTs of safinamide in people with Parkinson's disease of at least 3 years duration who were experiencing motor fluctuations. All participants were taking a stable dose of levodopa and many were also taking other Parkinson's disease medicines, most commonly a dopamine agonist (taken by 61% to 74% of participants). Study 016 (Borgohain et al. 2014a) and the SETTLE study (Schapira et al. 2016) were 24-week studies. Study 018 (Borgohain et al. 2014b) was an 18-month extension of study 016, although the primary outcome was different to the original study (see below). Study 016 included 2 treatment arms of safinamide 50 mg daily and 100 mg daily, while in the SETTLE study the starting dose of 50 mg daily was increased to 100 mg daily if no tolerability issues arose by day 14.

Motor symptoms and complications

In study 016 and the SETTLE study, safinamide increased on time without troublesome dyskinesia (the primary outcome) by approximately 30 to 60 minutes daily at 24 weeks (from a baseline of about 9 hours daily) compared with placebo. This improvement was considered clinically relevant in a population of people with advanced Parkinson's disease with motor fluctuations (EPAR: Xadago). In study 016, the mean difference with safinamide 50 mg compared with placebo was 0.51 hours (95% confidence interval [CI] 0.07 to 0.94, p=0.023); and with safinamide 100 mg it was 0.55 hours (95% CI 0.12 to 0.99, p=0.013). In SETTLE, the mean difference with safinamide 50–100 mg compared with placebo was 0.96 hours (95% CI 0.56 to 1.37, p<0.001). A similar reciprocal reduction in off time was also seen in both studies (see results tables for details).

The statistically significant improvement in on time without troublesome dyskinesia and off time was continued at 2 years in study 018 (although these were secondary outcomes). The mean

difference in on time without troublesome dyskinesia with safinamide 50 mg compared with placebo was 0.67 hours (95% CI 0.23 to 1.11, p=0.003); and with safinamide 100 mg it was 0.83 hours (95% CI 0.39 to 1.27, p=0.0002); with similar reciprocal reductions in off time seen.

A post-hoc analysis of pooled data from study 016 and the SETTLE study presented results of several sub-group analyses (Cattaneo et al. 2016). The subgroups were differentiated on whether or not participants were taking levodopa alone, or also using a dopamine agonist, COMT inhibitor or amantadine. The results presented for the outcomes of on time without troublesome dyskinesia and off time were broadly similar to the overall results for all subgroups.

In study 018 the primary outcome was change from baseline in Dyskinesia Rating Scale (DRS) total score (range 0 to 48 [personal communication: Profile Pharma November 2016]) during on time. No statistically significant difference in this outcome was seen with safinamide compared with placebo at 2 years. For safinamide 50 mg compared with placebo the mean difference in score was −0.51 (95%CI −1.32 to 0.29, p=0.213); and for safinamide 100 mg it was −0.59 (95%CI −1.40 to 0.21, p=0.147). In study 016 and the SETTLE study there were also no statistically significant improvements in DRS total score with safinamide compared with placebo (see results tables for details).

In study 016 and SETTLE, there were statistically significant improvements in motor symptoms with safinamide of about 2 points in UPDRS-III score (range 0 to 108) at 24 weeks (from a baseline of 22 to 29 points) compared with placebo. In study 016 the mean difference with safinamide 50 mg compared with placebo was −1.8 (95% CI −3.3 to −0.4, p=0.014); and with safinamide 100 mg it was −2.6 (95% CI −4.1 to −1.1, p=0.0006). The change in UPDRS-III score from baseline was −4.3, −6.1 and −6.9 in the placebo, 50 mg and 100 mg groups respectively. In SETTLE the mean difference with safinamide 50–100 mg compared with placebo was −1.82 (95%CI −3.01 to −0.62, p<0.003). The change in UPDRS score from baseline was −1.83 with placebo and −3.43 with safinamide 50–100 mg. An improvement of 2.5 to 5 points from baseline is considered to be the minimum clinically important difference (Schrag et al. 2006; Shulman et al. 2010).

In study 018, the improvement in UPDRS-III score was maintained with safinamide 100 mg daily (p<0.05), but there was no statistically significant difference between safinamide 50 mg daily and placebo at 2 years.

Health-related quality of life

In study 016 there was a statistically significant improvement in health-related quality of life of about 16 points in PDQ-39 total score (range 0 to 800 [personal communication: Profile Pharma

January 2017]) with safinamide 100 mg daily (p=0.036) compared with placebo at 24 weeks (from a baseline of about 230 points). However, there was no statistically significant difference in the 50 mg group compared with placebo (p=0.56). This result continued at 2 years in study 018 (see results tables for details).

In the SETTLE study, there was a statistically significant improvement of about 2 points in PDQ-39 summary index score (range 0 to 100) with safinamide 50–100 mg (from a baseline of about 27 points) compared with placebo. The mean difference was −2.33 (95%CI −3.98 to −0.68, p=0.006). A change of about 1.6 points relates to feeling 'a little worse' and is likely to represent a clinically important difference (Peto et al. 2001).

Clinical global impression

The percentage of participants with an improvement in clinical global impression (CGI-C) was significantly higher with safinamide compared with placebo at the end of both 24-week RCTs. In study 016, 55.4%, 66.4%, and 64.3% of participants in the placebo, 50 mg and 100 mg groups respectively had improvement (p=0.001 for safinamide 50 mg compared with placebo and p=0.009 for safinamide 100 mg compared with placebo). In SETTLE, 57.7% of participants had improvement with safinamide 50–100 mg compared with 41.8% of participants with placebo, odds ratio (OR) 1.92 (95%CI 1.36 to 2.70, p<0.001). In study 018, this statistically significant improvement was maintained in the safinamide 50 mg group, but not in the 100 mg group.

Activities of daily living

In study 016 and study 018, there was no statistically significant improvement in activities of daily living measured by UPDRS-II score (range 0 to 52) during on time with safinamide 50 mg daily compared with placebo at 24 weeks and at 2 years. In the safinamide 100 mg group, there was a statistically significant improvement of about 1 point compared with placebo (from a baseline of about 12 points) at 24 weeks (p=0.006) and at 2 years (p<0.05). In the SETTLE study, no statistically significant improvement in activities of daily living was observed with safinamide 50–100 mg compared with placebo.

An overview of the results for clinical effectiveness can be found in results tables.

Safety and tolerability

The SPC states that safinamide is contraindicated in people with severe hepatic impairment. It should also be used cautiously in people with moderate hepatic impairment at a maximum dose of

50 mg daily. Safinamide should be stopped if a person progresses from moderate to severe hepatic impairment.

Safinamide should not be used in people with an ophthalmological history that would put them at increased risk for potential retinal effects, for example, people with albinism, family history of hereditary retinal disease, retinitis pigmentosa, any active retinopathy, or uveitis (SPC: safinamide).

Impulse control disorders

Impulse control disorders can occur in people who are taking dopamine agonists or other dopaminergic medicines. There have been some reports of impulse control disorders occurring with other MAO inhibitors. The SPC states that safinamide has not been associated with any increase in the appearance of impulse control disorders. However, patients and carers should be made aware of the behavioural symptoms of these, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying (SPC: safinamide).

Dopaminergic adverse effects

The SPC states that when safinamide is used as an add-on treatment to levodopa it may potentiate the adverse effects of levodopa, and any pre-existing dyskinesia may be exacerbated, requiring a decrease in the dose of levodopa. However, it also states that dyskinesia occurred early in treatment, led to discontinuation in very few people, and did not require a reduction of dose in any person.

Dyskinesia was the most commonly reported adverse effect in the 3 RCTs, and was more frequent with safinamide compared with placebo. The percentage of participants experiencing dyskinesia in study 016 was 12.6%, 21.1%, and 18.3% in the placebo, 50 mg and 100 mg groups respectively. In study 018 this was 21.7%, 31.2% and 27.8% respectively. In the SETTLE study, 14.6% of participants experienced dyskinesia with safinamide 50–100 mg, compared with 5.5% in the placebo group.

Concomitant medicines

Safinamide is contraindicated for use with other MAO inhibitors (including moclobemide) due to the risk of hypertensive crisis. Concomitant use of safinamide and pethidine is also contraindicated, as serious adverse effects have been reported with other MAO inhibitors and this may be a class effect.

Concomitant use of fluoxetine or fluvoxamine should be avoided, but if necessary, they should be used at the lowest effective dose. Other antidepressants (selective serotonin reuptake inhibitors [SSRIs], serotonin norepinephrine reuptake inhibitors [SNRIs] and tricyclic or tetracyclic antidepressants) may be used with caution, but at the lowest doses necessary. Concomitant use of dextromethorphan is not recommended and sympathomimetics should be used with caution.

Safinamide can be used without any dietary tyramine restrictions.

For full information see the SPC for safinamide.

Tolerability

In study 016 there was no significant difference between treatment groups for the percentage of participants who experienced any adverse events (p=0.530) or discontinued treatment due to adverse events (p=0.850) at 24 weeks. There were significantly fewer serious adverse events in the safinamide 50 mg group, compared with either the placebo or 100 mg groups (p=0.029). There was no analysis of adverse event data in the SETTLE study or study 018, but there did not appear to be statistically significant differences between treatment groups in these studies.

The most commonly reported adverse reactions listed in the SPC (between 1 in 10 and 1 in 100 people) are dyskinesia, insomnia, nausea, somnolence, dizziness, headache, Parkinson's disease symptoms, cataracts, orthostatic hypotension and falls.

An overview of the results for safety and tolerability can be found in results tables.

Evidence strengths and limitations

The efficacy and safety of safinamide has been investigated in 3 placebo-controlled RCTs, which included a total of 1,218 participants (Borgohain et al. 2014a [study 016], Borgohain et al. 2014b [study 018] and Schapira et al. 2016 [SETTLE study]). The studies were double-blind and allocation was concealed.

An intention-to-treat analysis was used for efficacy outcomes. The safety analyses included all participants who had received at least 1 dose of study medicine. Withdrawal rates were relatively low in the 24-week studies and were similar across all treatment and comparison groups (11.2% in study 016 and 11.5% in SETTLE). In study 018, 19.1% of participants who enrolled did not complete the study, but these rates were similar across all groups.

Safinamide has not been compared with an active comparator in a head-to-head study, for example, other MAO-B inhibitors, dopamine agonists or COMT inhibitors. Therefore, the size of the effect is difficult to determine (EPAR: Xadago). A post-hoc analysis of pooled data from study 016 and the SETTLE study presented results of several sub-group analyses (Cattaneo et al. 2016). This showed that very few participants were taking levodopa alone at baseline (89/971, 9.2%). At baseline, 61% of participants in study 016 and 74% of participants in the SETTLE study were taking a dopamine agonist. There was also relatively high usage of anticholinergics in study 016 (37%), which is not likely to reflect UK practice. In the NICE guideline on Parkinson's disease, anticholinergics are not included as an option for adjuvant treatment in people with later Parkinson's disease.

The SETTLE study was conducted in North America and Europe and 68% of participants were Caucasian. However, studies 016 and 018 were predominantly conducted in India and the majority of participants (80%) were Asian. This is not reflective of the UK population and routine clinical practice is likely to be different from that in India.

Safinamide has not been investigated in people with:

- severe, disabling peak dose or biphasic dyskinesia with unpredictable or wide fluctuations
- history or presence of retinal disease
- psychiatric illness, bipolar disorder or severe depression (EPAR: Xadago).

In addition, there are no data on the long-term use (longer than 3 years) of safinamide, or use in people over the age of 75 years (EPAR: Xadago). The average age of participants recruited into the studies was 60 years in study 016 and 62 years in the SETTLE study. This may not be representative of people with mid- to late-stage Parkinson's disease who are experiencing motor fluctuations in real world practice. Participants also had to be able to adhere to strict daily requirements to keep a diary, and were excluded from the studies if they weren't able to do this.

Not all participants in study 016 continued into the 18-month extension study (study 018). People who had experienced clinically significant adverse events or had shown clinically significant deterioration in motor symptoms during study 016 were excluded from enrolling into study 18 (Borgohain et al. 2014b). This may overestimate the benefits and underestimate the harms of safinamide at 2 years, compared with placebo.

In study 018, there was no significant difference between either safinamide 50 mg or safinamide 100 mg and placebo in the primary outcome (DRS total score during on time). Therefore, caution is needed when interpreting the observed treatment effects on secondary outcomes. Two post-hoc

subgroup analyses have been published; 1 of pooled data from study 016 and the SETTLE study (Cattaneo et al. 2016) and 1 of data from study 018 (Cattaneo et al. 2015). However, these subgroups were not pre-specified in the original studies and the findings should be interpreted with caution.

An overview of the quality assessment of each included study can be found in evidence tables.

Estimated impact for the NHS

Other treatments

A range of adjuvant treatments are available for people with Parkinson's disease who are experiencing motor fluctuations on levodopa alone, including other MAO-B inhibitors (rasagiline and selegiline). Alternative adjuvant options include dopamine agonists (for example, pramipexole, ropinirole and rotigotine) and COMT inhibitors (for example, entacapone).

Costs of other treatments

See table 3 for the costs of other MAO-B inhibitors compared with safinamide.

Table 3 Costs of other treatments

Medicine	Usual dose[a]	30-day cost excluding VAT
Safinamide (Xadago)	50–100 mg daily	£69.00[b]
Rasagiline (generic)	1 mg daily	£3.38[b]
Selegiline (Eldepryl)	10 mg daily	£9.67[b]
Selegiline (Zelapar)	1.25 mg daily	£43.16[c]

[a] Doses shown do not represent the full range that can be used and do not imply therapeutic equivalence. Taken from the relevant SPC.

[b] Costs based on Drug Tariff, February 2017; excluding VAT.

[c] Costs based on MIMS, February 2017; excluding VAT.

Current or estimated usage

The manufacturer of safinamide has estimated likely uptake based on a share of adjuvant treatment for people with Parkinson's disease, in whom motor symptoms are not adequately controlled by an optimised dose of levodopa. Based on Office of National Statistics population data, Parkinson's UK prevalence data, and an estimated uptake of 15%, 25% and 35% of newly identified people in the first 3 years respectively, they estimate that 1,010, 1,690 and 2,360 people with Parkinson's disease will receive safinamide. This represents total annual costs of £849,000 in year 1, £1,416,000 in year 2 and £1,982,000 in year 3.

Likely place in therapy

Safinamide is the third MAO-B inhibitor licensed in the UK as add-on treatment to levodopa in people with Parkinson's disease who are experiencing motor fluctuations. The EPAR concluded that safinamide has a statistically significant and clinically relevant effect when added to levodopa and other Parkinson's disease medicines in people with mid- to late-stage Parkinson's disease.

The main benefits seen with safinamide in the 24-week RCTs were an increase in on time without troublesome dyskinesia of approximately 30 to 60 minutes, and a similar reciprocal reduction in off time. There were improvements in motor symptoms (measured by UPDRS-III during on time) and clinical global impression. Some other benefits were demonstrated with safinamide 100 mg daily, but not with 50 mg daily, for example improvements in health-related quality of life (measured by PDQ-39). The EPAR for safinamide states that a dose-response relationship was shown.

The EPAR concluded that safinamide has not been compared with other active treatments in a head-to-head trial, so no information is available on how its efficacy and safety compares with other treatments, particularly other MAO-B inhibitors. The EPAR states that indirect comparisons of data on safinamide with historical data on other treatments, such as rasagiline and pramipexole were considered favourable. In addition, a company sponsored meta-analysis and indirect comparison of placebo-controlled RCTs (Schnitker et al. 2015) of safinamide and entacapone as add-on treatment to levodopa has been published.

Although safinamide is licensed as add-on treatment to levodopa alone, very few participants in the studies were taking levodopa only (89/971, 9.2%; Cattaneo et al. 2016). Therefore, there are limited data on its use as a first-choice add-on treatment to levodopa.

The manufacturer applied for a marketing authorisation for treating early-stage Parkinson's disease in adults, as add-on treatment to a stable dose of a single dopamine agonist. The efficacy of

safinamide in early Parkinson's disease as add-on treatment to a dopamine agonist was considered to be not established and safinamide was not approved for this indication (EPAR: Xadago).

Overall, safinamide was generally well tolerated with a relatively low incidence of adverse events compared with placebo (EPAR: Xadago). The contraindications and cautions stated in the SPC for safinamide are similar to those of other MAO-B inhibitors, although there are some specific differences particularly compared with selegiline (see summaries of product characteristics for details). There is a concern about the risk of retinal degeneration with safinamide in people with a presence of, or history of, retinal disease that also needs to be considered (EPAR: Xadago).

Dyskinesia is a common and distressing complication for people with mid- to late-stage Parkinson's disease. Dyskinesia was the most commonly reported adverse effect in the studies, and the EPAR concluded that this could be considered as a risk for people treated with safinamide. No significant improvement in dyskinesia (measured by DRS total score) was observed with safinamide in any of the studies at any dose. The EPAR for safinamide states that claims of beneficial effects on dyskinesia could not be supported by the data. However, dyskinesias were usually mild and associated with an increase in on time. The SPC states that dyskinesia may occur on safinamide, and may worsen in people who have pre-existing dyskinesia.

Safinamide differs from other MAO-B inhibitors in its mode of action, as it also has additional activity at non-MAO-B targets. However, the EPAR concluded that at therapeutic concentrations, inhibition of brain MAO-B was the most likely mechanism responsible for the observed increase in on time. The evidence provided to the Committee for Medicinal Products for Human Use (CHMP) was not considered convincing enough for them to conclude that other non-MAO-B mechanisms of action were relevant for people treated with safinamide (EPAR: Xadago).

In addition to effectiveness, safety and patient factors, local decision makers will need to take cost into account when considering the likely place in therapy for safinamide. Safinamide is more expensive than other MAO-B inhibitors: 30-day treatment costs are £3.38, £9.67 and £69.00 for rasagiline, selegiline and safinamide respectively (Drug Tariff, February 2017; excluding VAT).

The NICE guideline on Parkinson's disease makes recommendations on the place in therapy of adjuvant treatments, including MAO-B inhibitors (see introduction and current guidance). The choice of treatment will depend on the person's clinical and lifestyle characteristics, and their preferences, after an informed discussion about the benefits and risks of treatment.

Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on NHS Choices.

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's good practice guidelines. These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?

- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?
- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

Relevance to other NICE programmes

NICE issued a guideline on Parkinson's disease in June 2006. This is currently being updated (publication expected April 2017).

This use of safinamide is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

References

Borgohain R, Szasz J, Stanzione P et al. (2014) Randomized trial of safinamide add-on to Levodopa in Parkinson's disease with motor fluctuations. Movement disorders 29: 229–37

Borgohain R, Szasz J, Stanzione P et al. (2014) Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. Movement disorders 29: 1273–80

Cattaneo C, Carlo F, Bonizzoni E et al. (2015) Long-term effects of safinamide on dyskinesia in mid- to late-stage Parkinson's disease: A post-hoc analysis. Journal of Parkinson's disease 5: 475–81

Cattaneo C, Sardina M, Bonizzoni E (2016) Safinamide as add on therapy to levodopa in mid- to late-stage Parkinson's disease fluctuating patients: Post-hoc analyses of studies 016 and SETTLE. Journal of Parkinson's disease 6: 165–73

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Schapira A, Fox S, Hauser R et al. (2016) Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations. A randomized clinical trial. JAMA Neurology doi:10.1001/jamaneurol.2016.4467

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Schnitker J, Müller T (2015) Meta-analysis of placebo-controlled clinical trials of safinamide and entacapone as add-on therapy to levodopa in the treatment of Parkinson's disease. European Neurological Review 10: 15–22

Shulman L, Gruber-Baldini A, Anderson K et al. (2010) The clinically important difference on the Unified Parkinson's Disease Rating Scale. JAMA Neurology 67: 64–70

Evidence tables

Table 4 Borgohain et al. 2014a (study 016)

Study reference	Borgohain R, Szasz J, Stanzione P et al. (2014) Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. Movement disorders 29: 229–37
Unique identifier	NCT01187966
Study type	RCT
Aim of the study	To evaluate the efficacy and safety of safinamide, as an add-on therapy to stable levodopa and other dopaminergic medicines in people with Parkinson's disease and motor fluctuations
Study dates	January 2007 to October 2008
Setting	India (35 centres), Romania (10 centres) and Italy (7 centres)
Number of participants	n=669 randomised[a]

Population	Adults aged 30 to 80 years with mid-to-late-stage Parkinson's disease, experiencing motor fluctuations while receiving levodopa and other dopaminergic medicines[b]. Mean age of randomised participants was 60 years; 72% were male and approximately 80% were Asian. Mean Hoehn and Yahr score was 2.8
Inclusion criteria	Idiopathic Parkinson's disease of at least 3 years' duration; Hoehn and Yahr stage I to IV during off time; motor fluctuations (>1.5 hours' off time/day). Participants also had to be able to accurately maintain a diary
Exclusion criteria	Late-stage Parkinson's disease if people experienced severe, disabling peak-dose or biphasic dyskinesia, or unpredictable or widely swinging symptom fluctuations. People with evidence of dementia, major psychiatric illnesses, or severe and progressive medical illnesses. Concomitant use of MAO inhibitors, tricyclic antidepressants and SNRIs
Intervention(s)	2 active treatment arms: • Safinamide 50 mg once daily (n=223) • Safinamide 100 mg once daily (n=224)
Comparator(s)	Placebo (n=222)
Length of follow up	24 weeks
Outcomes[c]	Primary outcome: • change in mean daily total on time without troublesome dyskinesia (recorded in patient diaries)

	Secondary outcomes: • total daily off time • UPDRS-III (motor) score during on time • CGI-C score • off time following the first morning levodopa dose • Dyskinesia Rating Scale (DRS) total score during on time • UPDRS-II (activities of daily living) score during on time • CGI-S score • % change in levodopa dose • GRID-HAM-D total score • PDQ-39 total score	
	Safety outcomes: • Any adverse events • Study drug-related adverse events • Serious adverse events • Withdrawals due to adverse events	
Source of funding	Newron and Merck Serono	
Overall risk of bias/quality assessment – CASP RCT checklist	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes[d]
	Were patients, health workers and study personnel blinded?	Yes
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes

	Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 7
	How precise was the estimate of the treatment effect?	See table 7
	Can the results be applied in your context? (or to the local population)	Unclear[e]
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See key points
Study limitations	• Approximately 80% of randomised participants were Asian • The population studied may be younger than people with mid- to late-Parkinson's disease seen in clinical practice • There was high usage of anticholinergics which is not likely to reflect current UK clinical practice • The intervention was not compared with an active comparator, for example another MAO-B inhibitor	

Comments

[a] Prior to randomisation Parkinson's disease treatments were optimised and a 28-day fixed dose period was required.

[b] Randomised participants were all taking levodopa, and many were also taking other Parkinson's disease medicines (see table below).

% of patients on treatment	Placebo	Safinamide 50 mg	Safinamide 100 mg
Levodopa	100	100	100
Dopamine agonist	62	64	57
Entacapone	25	23	25
Anticholinergic	39	33	39
Amantadine	15	13	13

[c] Change from baseline to week 24 for the primary outcome was analysed using a mixed linear model with baseline as a covariate. A sequence of comparisons approach was used for primary and secondary outcomes: safinamide 100 mg daily vs placebo was tested first, and if significant, safinamide 50 mg daily was tested versus placebo. Mixed model repeated measures (MMRM) analysis was used; in this analysis, there are no imputations for missing data. Sensitivity analyses were performed using the last observation carried forward (LOCF) analysis and an observed cases (OC) analysis. All 3 analyses produced similar results. Adverse effects were compared across groups using Cochran-Mantel-Haenszel test stratified by centre.

[d] Participants were randomised using a computer-generated randomisation schedule provided by the manufacturer and administered via a central interactive voice-response system.

[e] The study was conducted in India, Romania and Italy. Approximately 80% of randomised participants were Asian.

Abbreviations: CGI-C, Clinical Global Impression-Change; CGI-S, Clinical Global Impression-Severity; DRS, Dyskinesia Rating Scale; GRID-HAM-D, GRID Hamilton Rating Scale for Depression; MAO, Monoamine oxidase; PDQ-39, Parkinson's Disease Questionnaire (PDQ-39) subscale; RCT, Randomised controlled trial; SNRI, Serotonin-Norepinephrine Reuptake Inhibitor; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 5 Borgohain et al. 2014b (study 018)

Study reference	Borgohain R, Szasz J, Stanzione P et al. (2014) Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. Movement disorders 2: 1273–80
Unique identifier	NCT01286935
Study type	RCT (18-month extension study to study 016)
Aim of the study	To assess the long-term efficacy and safety of safinamide as an add-on to levodopa in people with mid- to late-Parkinson's disease and motor fluctuations
Study dates	August 2007 to April 2010
Setting	India (35 centres), Romania (10 centres) and Italy (7 centres)
Number of participants	n=669 randomised[a]; 544 enrolled into this study. 50/594 participants who completed study 016 did not enrol in this study
Population	Adults aged 30 to 80 years with mid-to-late-stage Parkinson's disease, experiencing motor fluctuations while receiving levodopa and other dopaminergic medicines who had completed study 016 (see table 4)
Inclusion criteria	Completion of study 016, treatment compliant and willing to continue, or people who had discontinued from study 016 but had completed scheduled efficacy evaluations at weeks 12 and 24
Exclusion criteria	People who had experienced clinically significant adverse events or shown clinically significant deterioration in motor symptoms during study 016
Intervention(s)	2 active treatment arms: • Safinamide 50 mg once daily (randomised in study 016, n=223; enrolled in study 018, n=189) • Safinamide 100 mg once daily (randomised in study 016, n=224; enrolled in study 018, n=180) Participants continued in the same treatment group to which they were randomised in study 016
Comparator(s)	Placebo (randomised in study 016, n=222; enrolled in study 018, n=175)

Length of follow up	2 years from randomisation (18-month extension of study 016)
Outcomes[b]	Primary outcome: • Mean change in Dyskinesia Rating Scale (DRS) total score during on time Note: the primary outcome is different to the original 24-week study (study 016)
	Secondary outcomes: • change in mean daily total on time without troublesome dyskinesia (recorded in patient diaries) • diary responder rates • UPDRS-IV (complications of therapy) total score and scores of 32 to 35 (dyskinesia and dystonia) and 32 to 34 (dyskinesia) • UPDRS-II (activities of daily living) score during on time • UPDRS-II response rates • UPDRS-III (motor) score during on time • change in levodopa dose • CGI-C score • CGI-S score • change in individual diary categories (on with no dyskinesia, on without troublesome dyskinesia, on with troublesome dyskinesia, off, asleep) • GRID-HAM-D total score • PDQ-39 total score
	Safety outcomes: • Any adverse events • Serious adverse events • Withdrawals due to adverse events

Source of funding	Newron and Merck Serono	
Overall risk of bias/quality assessment – CASP RCT checklist	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes[c]
	Were patients, health workers and study personnel blinded?	Yes
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 8
	How precise was the estimate of the treatment effect?	See table 8
	Can the results be applied in your context? (or to the local population)	Unclear[d]
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See key points

Study limitations	• Approximately 80% of randomised participants were Asian • The population studied may be younger than people with mid- to late-Parkinson's disease seen in clinical practice • There was high usage of anticholinergics which is not likely to reflect current UK clinical practice • The intervention was not compared with an active comparator, for example another MAO-B inhibitor • The study excluded people who had experienced clinically significant adverse events or had shown clinically significant deterioration in motor symptoms during study 016. This may overestimate the benefits and underestimate the harms of safinamide at 2 years, compared with placebo
Comments	[a] Prior to randomisation PD treatments were optimised and a 28-day fixed dose period was required. [b] People in the treatment and placebo arms were all taking levodopa, and many were also taking other Parkinson's disease medicines (see table 4). [c] Change from baseline to endpoint for the primary outcome was analysed using a mixed linear model with baseline as a covariate. A sequence of comparisons approach was used for primary and secondary outcomes: safinamide 100 mg daily vs placebo was tested first, and if significant, safinamide 50 mg daily was tested versus placebo. Adverse effects were compared across groups using Cochran-Mantel-Haenszel test stratified by centre. [d] Participants were randomised using a computer-generated randomisation schedule provided by the manufacturer, and administered via a central interactive voice-response system. [e] The study was conducted in India, Romania and Italy. Approximately 80% of randomised patients were Asian.
Abbreviations: CGI-C, Clinical Global Impression-Change; CGI-S, Clinical Global Impression-Severity; DRS, Dyskinesia Rating Scale; GRID-HAM-D, GRID Hamilton Rating Scale for Depression; PDQ-39, Parkinson's Disease Questionnaire; RCT, Randomised controlled trial; UPDRS, Unified Parkinson's disease Rating Scale.	

Table 6 Schapira et al. 2016 (SETTLE study)

Study reference	Schapira A, Fox S, Hauser R, et al. (2016) Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations. A randomized clinical trial. JAMA Neurology doi:10.1001/jamaneurol.2016.4467
Unique identifier	NCT00627640
Study type	RCT
Aim of the study	To investigate the efficacy and safety of safinamide in levodopa-treated people with motor fluctuations
Study dates	February 2009 to March 2012
Setting	21 countries in Europe, the Asia-Pacific region and North America (126 centres)
Number of participants	n=549 randomised[a]
Population	Adults aged 30 to 80 years with Parkinson's disease, experiencing motor fluctuations while receiving levodopa and other dopaminergic medicines[b]. Mean age of randomised participants was 62 years; 61% were male and 68% were Caucasian. Mean Hoehn and Yahr score was 2.5
Inclusion criteria	Idiopathic Parkinson's disease of at least 3 years' duration; Hoehn and Yahr stage I-IV during off time; motor fluctuations (>1.5 hours' off time/day, excluding morning akinesia); responsive to levodopa; if female, be either post-menopausal for ≥2 years, surgically sterilised (or have undergone hysterectomy), or willing to use an adequate method of contraception. Patients also had to be able to accurately maintain a diary

Exclusion criteria[c]	Exclusion criteria included: people experiencing severe, disabling peak-dose or biphasic dyskinesia, or unpredictable or widely swinging symptom fluctuations. People with other diagnoses of a clinically significant medical condition; clinically significant abnormalities by physical examination, electrocardiography, or laboratory tests; severe dizziness or fainting on standing, due to postural hypotension; history of retinal disease or severely diminished visual acuity; current or recent drug or alcohol abuse, psychosis, dementia, cognitive dysfunction or depression; history of hypersensitivity or contraindications to levodopa, other Parkinson's disease medicines, anticonvulsants, or drugs similar to safinamide. Concomitant use of some medicines, including MAO inhibitors, opioids, tricyclic antidepressants and SNRIs
Intervention(s)	Safinamide 50 to 100 mg once daily (n=274) Patients started treatment on 50 mg daily and increased to 100 mg daily if there were no tolerability issues by day 14. Over 90% of patients were receiving the 100 mg dose at day 14
Comparator(s)	Placebo (n=275)
Length of follow up	24 weeks
Outcomes	Primary outcome: change in mean daily total on time without troublesome dyskinesia (recorded in patient diaries)

	Secondary outcomes (not an exhaustive list): • total daily off time • UPDRS-II (activities of daily living) score during on time • UPDRS-III (motor) score during on time • CGI-C (% of patients with improvement and total score) • PDQ-39 summary index score • Dyskinesia Rating Scale (DRS) total score during on time • UPDRS-IV (complications of therapy) total score and score of 32 to 35 (dyskinesia and dystonia) and 32 to 34 (dyskinesia) • change in levodopa dose • CGI-S score • PGI-C score • EQ-5D score	
	Safety outcomes: • Any adverse events • Study drug-related adverse events • Serious adverse events • Withdrawals due to adverse events	
Source of funding	Newron and Merck Serono	
Overall risk of bias/quality assessment – CASP RCT checklist	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes[d]
	Were patients, health workers and study personnel blinded?	Yes
	Were the groups similar at the start of the trial?	Yes

	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 9
	How precise was the estimate of the treatment effect?	See table 9
	Can the results be applied in your context? (or to the local population)	Yes
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	see key points
Study limitations	• The population studied may be younger than people with mid- to late-Parkinson's disease seen in clinical practice • The intervention was not compared with an active comparator, for example another MAO-B inhibitor	

<table>
<tr><td>Comments</td><td>[a] Prior to randomisation there was an observation phase for 4 weeks or longer to allow 4-week observation of an unchanged regimen. Participants still needed to be experiencing daily off time >1.5 hours at the end of the 4-week observation period.
[b] People in the treatment and placebo arms were all taking levodopa, and many were also taking other Parkinson's disease medicines (see table below). Participants needed to be stabilised on these medicines in the 4 weeks prior to randomisation.
[c] Not all data presented in the published paper. Full exclusion criteria are summarised in the online supplement.
[d] Participants were randomised using a computer-generated randomisation schedule provided by the manufacturer, and administered via a central interactive voice-response system. The randomisation code remained blinded throughout the study.
<table>
<tr><th></th><th>Total % of patients on treatment</th></tr>
<tr><td>Levodopa</td><td>100</td></tr>
<tr><td>Dopamine agonist</td><td>74</td></tr>
<tr><td>Entacapone</td><td>15</td></tr>
<tr><td>Anticholinergic</td><td>17</td></tr>
<tr><td>Amantadine</td><td>30</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Abbreviations: CGI-C, Clinical Global Impression-Change; CGI-S, Clinical Global Impression-Severity; DRS, Dyskinesia Rating Scale; EQ-5D, EuroQoL 5 dimension score; PDQ-39, Parkinson's Disease Questionnaire; PGI-C, Patient Global Impression-Change; RCT, Randomised controlled trial; UPDRS, Unified Parkinson's disease Rating Scale.</td></tr>
</table>

Results tables

Table 7 Borgohain et al. 2014a (study 016)

	Placebo	Safinamide 50 mg	Safinamide 100 mg	Analysis (mean difference vs placebo)[a]
n (randomised)	222	223	224	

Primary outcome[b]				
Mean change from baseline in daily on time without troublesome dyskinesia (hours)	+0.72[c] (from mean baseline of 9.30)	+1.23 (from mean baseline of 9.37)	+1.28 (from mean baseline of 9.52)	50 mg: 0.51 (95% CI 0.07 to 0.94), p=0.0223 100 mg: 0.55 (95% CI 0.12 to 0.99), p=0.013
Selected secondary outcomes[b]				
Mean change from baseline in daily off time (hours)	−0.7 (from mean baseline of 5.3)	−1.3 (from mean baseline of 5.2)	−1.3 (from mean baseline of 5.2)	50 mg: −0.6 (95% CI −0.9 to −0.2), p=0.0043 100 mg: −0.6 (95% CI −1.0 to −0.2), p=0.0034
Mean change from baseline in DRS[d] total score	−0.2 (from mean baseline of 3.4)	−0.3 (from mean baseline of 3.9)	−0.3 (from mean baseline of 3.7)	50 mg: p=0.181, NS 100 mg: p=0.243, NS
Mean change from baseline in UPDRS-III[d] motor score	−4.3 (from mean baseline of 28.7)	−6.1 (from mean baseline of 27.3)	−6.9 (from mean baseline of 28.3)	50 mg: −1.8 (95% CI −3.3 to −0.4), p=0.014 100 mg: −2.6 (95% CI −4.1 to −1.1), p=0.0006
Mean change from baseline in UPDRS-II[d] ADL score	−1.2 (from mean baseline of 12.3)	−1.7 (from mean baseline of 11.8)	−2.2 (from mean baseline of 12.1)	50 mg: p=0.125, NS 100 mg: p=0.006
CGI-C (% of patients with improvement)	55.4	66.4	64.3	50 mg: p=0.001 100 mg: p=0.009
Mean change from baseline in PDQ-39 total score	−11.9 (from mean baseline of 230)	−16.4 (from mean baseline of 225)	−28.4 (from mean baseline of 229)	50 mg: p=0.56, NS 100 mg: p=0.036
Safety and tolerability outcomes[e]				
n (randomised)	**222**	**223**	**224**	

Participants with any adverse events	68.5% (152/222)	65.9% (147/223)	65.6% (147/224)	p=0.529[f], NS
Participants with study drug-related adverse events	23.0% (51/222)	30.9% (69/223)	29.9% (67/224)	p=0.140[f], NS
Participants with serious adverse events	8.1% (18/222)	3.6% (8/223)	9.8% (22/224)	Significantly higher in placebo and 100 mg groups, compared with 50 mg group p=0.029[f]
Participants discontinued due to adverse events	5.4% (12/222)	4.9% (11/223)	6.3% (14/224)	p=0.850[f], NS
Dyskinesia	12.6% (28/222)	21.1% (47/223)	18.3% (41/224)	Not reported

[a] All values are least-squares mean difference in change from baseline to 24 weeks (end of the study).

[b] Intention to treat population included all randomised participants and was used for all efficacy outcomes. If a patient's dose of levodopa or other Parkinson's disease medicines was increased by ≥20%, or if rescue medication was used, data were censored at that point and week 24 evaluations were carried out before the intervention ('on treatment' analysis).

[c] Data from EPAR: Xadago.

[d] Outcome measured during on time.

[e] The safety population was all participants who received at least 1 dose of study medication and had a subsequent safety assessment.

[f] Interaction of the 3 groups using the Cochran-Mantel-Haenszel test.

Abbreviations: ADL, Activities of daily living; CI, Confidence interval; NS, Not statistically significant.

Table 8 Borgohain et al. 2014b (study 018)

	Placebo	Safinamide 50 mg	Safinamide 100 mg	Analysis (mean difference vs placebo)[a]
n (randomised)	222	223	224	

Primary outcome[b]				
Mean change from baseline in DRS total score[c]	+0.32 (from mean baseline of 3.4)	−0.19 (from mean baseline of 3.9)	−0.28 (from mean baseline of 3.7)	50 mg: −0.51 (95% CI −1.32 to 0.29), p=0.213, NS 100 mg: −0.59 (95% CI −1.40 to 0.21), p=0.147, NS
Selected secondary outcomes[b]				
Mean change from baseline in daily on time without troublesome dyskinesia (hours)	+0.34 (from mean baseline of 9.30)	+1.01 (from mean baseline of 9.37)	+1.18 (from mean baseline of 9.52)	50 mg: 0.67 (95% CI 0.23 to 1.11), p=0.003 100 mg: 0.83 (95% CI 0.39 to 1.27), p=0.0002
Mean change from baseline in daily off time (hours)	−0.74[d] (from mean baseline of 5.3)	−1.36[d] (from mean baseline of 5.2)	−1.49[d] (from mean baseline of 5.2)	50 mg: −0.62 (95% CI −0.98 to −0.25), p=0.001 100 mg: −0.75 (95% CI −1.11 to −0.38), p<0.0001
Mean change from baseline in UPDRS-III[c] motor score	−3.94[d] (from mean baseline of 28.7)	−4.98[d] (from mean baseline of 27.3)	−6.06[d] (from mean baseline of 28.3)	50 mg: −1.05 (95% CI −2.58 to 0.48)[e], NS 100 mg: −2.13 (95% CI −3.65 to −0.60)[e], p<0.05
Mean change from baseline in UPDRS-II[c] ADL score	−0.91[d] (from mean baseline of 12.3)	−1.43[d] (from mean baseline of 11.8)	−1.97[d] (from mean baseline of 12.1)	50 mg: −0.52 (95% CI −1.29 to 0.25)[e], NS 100 mg: −1.06 (95% CI −1.83 to −0.29)[e], p<0.05

CGI-C (% of patients with improvement)	53.6[c]	62.3[c]	59.8[c]	50 mg: p=0.009[d] 100 mg: p=0.063[d], NS
Mean change from baseline in PDQ-39 total score	−13.65[c] (from mean baseline of 230)	−24.12[c] (from mean baseline of 225)	−32.01[c] (from mean baseline of 229)	50 mg: −10.48 (95% CI −25.94 to 4.98)[e], p=0.184[d] 100 mg: −18.36 (95% CI −33.75 to −2.97)[e], p=0.020[d]
Safety and tolerability outcomes[f]				
n	175	189	180	
Participants with any adverse events	91.4% (160/175)	88.9% (168/189)	90.6% (163/180)	p=0.45[d], NS
Participants with serious adverse events	16.0% (28/175)	16.9% (32/189)	18.9% (34/180)	p=0.81[d], NS
Participants discontinued due to adverse events	5.7% (10/175)	5.3% (10/189)	6.7% (12/229)	Not reported
Dyskinesia	21.7% (38/175)	31.2% (59/189)	27.8% (50/229)	Not reported

[a] All values are least-squares mean difference in change from baseline to 2 years (end of the study), unless otherwise stated. Baseline was the start of study 016.

[b] Intention to treat population included all randomised participants and was used for all efficacy outcomes. If a person's dose of levodopa or other Parkinson's disease medicines was increased by ≥20%, or if rescue medication was used, data were censored at that point and week 24 evaluations were carried out before the intervention ('on treatment' analysis).

[c] Outcome measured during on time.

[d] Data provided by Profile Pharma, personal communication December 2016.

[e] Data from EPAR: Xadago.

[f] The safety population was all participants who received at least 1 dose of study medication and had a subsequent safety assessment, from the start of study 016.

Abbreviations: ADL, Activities of daily living; CI, Confidence interval; NS, Not statistically significant.

Table 9 Schapira et al. 2016 (SETTLE study)

	Placebo	Safinamide 50–100 mg	Analysis (mean difference vs placebo)[a]
N (randomised)	275	274	
Primary outcome[b]			
Mean change from baseline in daily on time without troublesome dyskinesia (hours)	+0.57 (from mean baseline of 9.06)	+1.42 (from mean baseline of 9.30)	0.96 (95% CI 0.56 to 1.37), p<0.001
Selected secondary outcomes[b]			
Mean change from baseline in daily off time (hours)	−0.54 (from mean baseline of 5.38)	−1.56 (from mean baseline of 5.34)	−1.03 (95% CI −1.40 to −0.67), p<0.001
Mean change from baseline in DRS[c] total score	−0.24 (from mean baseline of 2.57)	−0.11 (from mean baseline of 2.79)	0.23 (95% CI −0.14 to 0.60), p=0.22, NS
Mean change from baseline in UPDRS-III[c] motor score	−1.83 (from mean baseline of 23.05)	−3.43 (from mean baseline of 22.26)	−1.82 (95% CI −3.01 to −0.62), p=0.003
Mean change from baseline in UPDRS-II[c] ADL score	−0.75 (from mean baseline of 10.43)	−1.07 (from mean baseline of 9.97)	−0.43 (95% CI −1.02 to 0.16), p=0.15, NS
CGI-C (% of patients with improvement)	41.8	57.7	OR 1.92 (95% CI 1.36 to 2.70), p<0.001
Mean change from baseline in PDQ-39 summary index score	−0.68 (from mean baseline of 26.94)	−3.17 (from mean baseline of 27.47)	−2.33 (95% CI −3.98 to −0.68), p=0.006
Safety and tolerability outcomes[d]			
n	275	274	

Participants with any adverse events	69.1% (190/275)	67.9% (186/274)	p=0.78[e], NS
Participants with study drug-related adverse events	27.6% (76/275)	28.5% (78/274)	P=0.850[e], NS
Participants with serious adverse events	9.5% (26/275)	6.6% (18/274)	P=0.271[e], NS
Participants discontinued due to adverse events	3.6% (10/275)	4.4% (12/274)	P=0.430[e], NS
Dyskinesia	5.5% (15/275)	14.6% (40/274)	P<0.001[e]
[a] All values are least-squares mean difference in change from baseline to 24 weeks (end of the study), unless otherwise stated. [b] Intention to treat population included all randomised participants. For patients who discontinued or changed their Parkinson's disease medication, a week-24 value was imputed by a last observation carried forward approach. [c] Outcome measured during on time. [d] The safety population was all participants who were exposed to study medication. [e] Data provided by Profile Pharma, personal communication December 2016.			
Abbreviations: ADL, Activities of daily living; CI, Confidence interval; NS, Not statistically significant; OR, Odds ratio.			

Excluded studies

Study reference	Reason for exclusion
Anand R, Barone P, Schapira A et al. (2013) Safinamide is effective as add-on treatment in both early and advanced PD. Journal of the neurological sciences 333: e69	Abstract only
Anand R, Borgohain R, Stocchi F et al. (2012) First 2-year, placebo-controlled study in Parkinson's disease patients with motor fluctuations indicates safinamide may benefit patients with more severe dyskinesia. Parkinsonism and related disorders 18: S132–S133	Abstract only

Barone P, Cattaneo C, Bonizzoni E et al. (2015) Safinamide significantly reduces pain treatments when given as add-on therapy to levodopa in patients with Parkinson's disease and fluctuations. Movement Disorders 30: S150	Abstract only
Barone P, Cattaneo C, La Ferla R et al. (2015) Significant reduction of pain treatments with safinamide administered as add-on therapy to levodopa in patients with Parkinson's disease and fluctuations. European Journal of Neurology 22: 293	Abstract only
Bonizzoni E, Gambini F, Sardina M et al. (2014) Bootstrap analysis of ON and OFF time data in the SETTLE study. Movement Disorders 29: S228	Abstract only
Cattaneo C, Bonizzoni E, Sardina M et al. (2015) Efficacy of safinamide as adjunct therapy in mid- to late-stage fluctuating Parkinson's disease patients: Post-hoc analyses of 016 and SETTLE trials. Movement Disorders 30: S75	Abstract only
Cattaneo C, Bonizzoni E, La Ferla R et al. (2015) Favourable effect of safinamide on dyskinesia evolution over 2-year treatment of fluctuating Parkinson's disease patients. European Journal of Neurology 22: 247	Abstract only
Cattaneo C, La Ferla R, Bonizzoni E et al. (2015) Long-term effects of safinamide on dyskinesia in mid- to late-stage Parkinson's disease: a post-hoc analysis. Journal of Parkinson's disease 5: 475–81	Study not prioritised (not the best available evidence – post-hoc analysis of an included study)
Cattaneo C, Sardina M, Bonizzoni E et al. (2016) Safinamide as add-on therapy to levodopa in mid- to late-stage Parkinson's disease fluctuating patients: Post-hoc analyses of studies 016 and SETTLE. Journal of Parkinson's disease 6: 165–73	Study not prioritised (not the best available evidence – post-hoc analysis of an included study)
Martinez-Martin P, Rodriguez-Blazquez C, Forjaz M et al. (2015) Impact of pharmacotherapy on quality of life in patients with Parkinson's disease. CNS drugs 29: 397–413	Not a relevant study

Stocchi F, Arnold G, Onofrj M et al. (2004) Improvement of motor function in early Parkinson disease by safinamide. Neurology 63: 746–48	Not a relevant study
Stocchi F, Vacca L, Grassini P et al. (2006) Symptom relief in Parkinson disease by safinamide: biochemical and clinical evidence of efficacy beyond MAO-B inhibition. Neurology 67(7 Suppl 2): S24–S29	Not a relevant study

Terms used in this evidence summary

Clinical Global Impression-Change (CGI-C)

The Clinical Global Impression-Change (CGI-C) measures the change in clinical global impression relative to a baseline state at the beginning of the study. This change is rated as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. Patients with 'improvement' are those rated as very much improved, much improved or minimally improved.

Dyskinesia Rating Scale (DRS)

The Dyskinesia Rating Scale measures dyskinesia, with lower scores indicating less severe or less disabling dyskinesia. See Goetz et al. (1994) for more information. DRS total scores range from 0 to 48 (personal communication: Profile Pharma November 2016), but the minimal clinically important difference is unclear.

On and off time

People with Parkinson's disease can experience motor fluctuations (particularly when the dose of levodopa begins to wear off), which they often describe as being turned 'on' and 'off'. On and off time was recorded in patient diaries in the RCTs. Patients reported whether they were: 'on' with no dyskinesia, 'on' with no troublesome dyskinesia (not interfering with function or causing meaningful discomfort), 'on' with troublesome dyskinesia, 'off' (lack of mobility [bradykinesia or akinesia]), or asleep.

Parkinson's Disease Questionnaire (PDQ-39)

The Parkinson's Disease Questionnaire (PDQ-39) is a 39-item patient-reported rating scale that measures Parkinson's disease-specific health related quality of life. It covers 8 areas: mobility, activities of daily living (ADL), emotional well-being, stigma, social support, cognition, communication and bodily discomfort. Lower scores indicate better health related quality of life. PDQ-39 total scores range from 0 to 800 (personal communication: Profile Pharma January 2017). The total score can be summarised into the PDQ-39 summary index score (range of scores 0 to 100). A mean change in the PDQ-39 summary index score of about 1.6 points relates to feeling 'a little worse' and is likely to represent a clinically important difference. See Peto et al. (2001) for more information.

UPDRS-III

UPDRS-III is the Unified Parkinson's Disease Rating Scale – motor subscale. Lower scores indicate fewer motor symptoms. UPDRS-III scores range from 0 to 108. The minimal clinically important difference on the UPDRS-III is likely to be a reduction in score from baseline of about 2.5 to 5 points (Schrag et al. 2006; Shulman et al. 2010).

UPDRS-II

UPDRS-II is the Unified Parkinson's Disease Rating Scale – activities of daily living subscale. Lower scores are better and range from 0 to 52. The minimal clinically important difference on the UPDRS-II is likely to be a reduction in score of about 2 points (Hauser et al. 2014).

Search strategy

Medline (1946-present), Medline in-process; Medline Epubs Ahead of Print and Medline Daily update

Search date: 25th August 2016

1 exp Parkinsonian Disorders/ (65729)

2 parkinson*.tw. (90404)

3 1 or 2 (100470)

4 safinamide.tw. (78)

5 xadago.tw. (2)

6 "EMD-1195686".tw. (0)

7 EMD1195686.tw. (0)

8 "FCE-26743".tw. (6)

9 FCE26743.tw. (0)

10 4 or 5 or 6 or 7 or 8 or 9 (83)

11 3 and 10 (54)

Embase (1974 to 25th August 2016)

Search date: 26th August 2016

1 exp Parkinson disease/ (116362)

2 parkinson*.tw. (122252)

3 1 or 2 (149623)

4 safinamide.tw. (145)

5 xadago.tw. (13)

6 "EMD-1195686".tw. (1)

7 EMD1195686.tw. (0)

8 "FCE-26743".tw. (10)

9 FCE26743.tw. (0)

10 safinamide/ (275)

11 4 or 5 or 6 or 7 or 8 or 9 or 10 (289)

12 3 and 11 (213)

Cochrane library databases

Search date: 26th August 2016

#1 MeSH descriptor: [Parkinsonian Disorders] explode all trees

#2 Parkinson*:ti,ab

#3 #1 or #2

#4 safinamide:ti,ab

#5 xadago:ti,ab

#6 "EMD-1195686":ti,ab

#7 EMD1195686:ti,ab

#8 "FCE-26743":ti,ab

#9 FCE26743:ti,ab

#10 #4 or #5 or #6 or #7 or #8 or #9

#11 #3 and #10

Development of this evidence summary

The evidence summary: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Sundus Alusi: None

Dr Christopher Kobylecki: Honoraria for delivering educational meetings from Ipsen and UCB Pharma. Travel support to attend international meetings from Britannia Pharmaceuticals

About this evidence summary

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.

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